
Dewhurst's Textbook of Obstetrics & Gynaecology

EDITED BY

D. KEITH EDMONDS

FRCOG, FRACOG

Consultant Obstetrician and Gynaecologist

Queen Charlotte's and Chelsea Hospital

Goldhawk Road

London, UK

SEVENTH EDITION

DEWHURST'S TEXTBOOK OF
OBSTETRICS & GYNAECOLOGY

Dedication

This book is dedicated to my wife, Gill, and my children, Alastair, Nicholas and Timothy and to the memory of Sir Jack Dewhurst.

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Contents

- Contributors, vii
- Professor Sir John Dewhurst, xi
- Preface to the Seventh Edition, xii
- Preface to the First Edition, xiii
- 1 Clinical anatomy of the pelvis and reproductive tract, 1
Alan Farthing
- 2 Maternal physiology, 10
Fiona Broughton-Pipkin
- 3 The placenta and fetal membranes, 19
Berthold Huppertz and John C.P. Kingdom
- 4 Normal fetal growth, 28
Jason Gardosi
- 5 Pre-conception counselling, 34
Andrew McCarthy
- 6 Antenatal care, 39
Timothy G. Overton
- 7 Normal labour, 46
A.A. Calder
- 8 Fetal monitoring during labour, 56
James A. Low
- 9 Analgesia and anaesthesia, 63
John A. Crowhurst
- 10 Puerperium and lactation, 69
D. Keith Edmonds
- 11 Neonatal care for obstetricians, 81
M.A. Thomson and A.D. Edwards
- 12 Spontaneous miscarriage, 94
Joanne Topping and Roy G. Farquarson
- 13 Recurrent miscarriage, 100
Raj Rai
- 14 Ectopic pregnancy, 106
Davor Jurkovic
- 15 Trophoblast disease, 117
Philip Savage and Michael Seckl
- 16 Prenatal diagnosis and genetics, 125
Sailesh Kumar
- 17 Fetal medicine in clinical practice, 132
R.C. Wimalasundera
- 18 Obstetric emergencies, 145
Sara Paterson-Brown
- 19 Disorders of fetal growth and assessment of fetal well-being, 159
G.C.S. Smith and C.C. Lees
- 20 Multiple pregnancy, 166
Nicholas M. Fisk
- 21 Preterm labour, 177
Phillip Bennett
- 22 Prolonged pregnancy, 192
Patricia Crowley
- 23 Induction and augmentation of labour, 205
G. Justus Hofmeyr
- 24 Malpresentation, malposition, cephalopelvic disproportion and obstetric procedures, 213
S. Arulkumaran
- 25 Hypertensive disorders, 227
Andrew Shennan
- 26 Heart disease in pregnancy, 236
Catherine Nelson-Piercy
- 27 Diabetes and endocrine disease in pregnancy, 246
Anne Dornhorst and Catherine Williamson

- 28 Renal disease, 260
John Davison
- 29 Haematological problems in pregnancy, 270
P. Clark, A.J. Thomson and I.A. Greer
- 30 Miscellaneous medical disorders, 282
Andrew McCarthy
- 31 Obstetric statistics, 289
Jim G. Thornton
- 32 Contraception, 299
Anna Glasier
- 33 Termination of pregnancy, 318
Gillian Flett and Allan Templeton
- 34 Normal and abnormal development of the genital tract, 327
D. Keith Edmonds
- 35 The menstrual cycle, 348
William L. Ledger
- 36 The role of ultrasound in gynaecology, 356
Joanne Topping
- 37 Gynaecological disorders of childhood and adolescence, 364
D. Keith Edmonds
- 38 Primary amenorrhoea, 369
D. Keith Edmonds
- 39 Polycystic ovary syndrome and secondary amenorrhoea, 377
Adam H. Balen
- 40 Menstrual problems: menorrhagia and primary dysmenorrhagia, 399
Margaret C.P. Rees
- 41 Premenstrual syndrome, 408
P.M.S. O'Brien
- 42 Pelvic infection, 414
Jonathan D.C. Ross and Peter Stewart
- 43 Chronic pelvic pain, 423
R. William Stones
- 44 Endometriosis, 430
Stephen Kennedy and Philippe Koninckx
- 45 Infertility, 440
Siladitya Bhattacharya
- 46 Assisted reproduction, 461
Geoffrey Trew
- 47 Menopause and the postmenopausal woman, 479
Nick Panay
- 48 Pelvic floor dysfunction I: uterovaginal prolapse, 496
Anthony R.B. Smith
- 49 Urinary incontinence, 504
D. Robinson and L. Cardozo
- 50 Hysteroscopy and laparoscopy, 560
Adam Magos
- 51 Benign disease of the vulva, 578
Richard Staughton
- 52 Malignant disease of the vulva and the vagina, 591
David M. Luesley
- 53 Benign diseases of the vagina, cervix and ovary, 606
D. Keith Edmonds
- 54 Premalignant and malignant disease of the cervix, 614
Mahmood I. Shafi
- 55 Epithelial ovarian cancer, 625
Hani Gabra
- 56 Benign disease of the uterus, 636
Mary Ann Lumsden
- 57 Cancer of the uterine corpus, 645
Henry C. Kitchener
- 58 Sexual dysfunction, 651
Fran Reader
- 59 Ethical dilemmas in obstetrics and gynaecology, 658
Gordon M. Stirrat
- 60 The law and the obstetrician and gynaecologist, 684
Bertie Leigh
- 61 Domestic violence and sexual assault, 692
Maureen Dalton
- Index, 699
- Plate section can be found facing p. 562*

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Professor Sir John Dewhurst

Professor Sir John Dewhurst died on the 1st December 2006. Jack, as he was known to all his colleagues, was a doyen amongst obstetricians and gynaecologists of the twentieth century. His reputation was internationally renowned and he became a worldwide expert in paediatric and adolescent gynaecology for which he received due accolade. He was also an outstanding teacher of obstetrics and gynaecology and as such this textbook that he began in the 1970s is testament to his

dedication to the passing on of knowledge to others. In 1976 he became President of the Royal College of Obstetricians and Gynaecologists, a post he held for three years, for which he was subsequently knighted. He retired in 1986 after a long and distinguished career but his legacy lives on and he will be remembered by all who knew him with great affection and professional respect.

D. KEITH EDMONDS

Preface to the Seventh Edition

As I write this Preface in 2006, the specialty of obstetrics and gynaecology worldwide is going through a crisis of recruitment. It seems to all the contributors to this book a strange and sad time as the fascination of obstetrics and gynaecology remains unchallenged. Since the 6th edition, many advances have occurred and these have led to improvements in healthcare throughout the world. The efforts with regard to maternal and fetal health and to the gynaecological care of women remains a triumph of modern medicine. We hope that the reader will enjoy being stimulated by the fascination and intellectual stimulation that comes from the study of obstetrics and gynaecology.

I wish to thank all the contributors who have submitted chapters for the readers' pleasure, to impart their knowledge and to hopefully see this translated into high quality clinical practice.

I would like to thank all of the contributors whose contributions span the breadth of obstetrics and gynaecology and we hope that these individual chapters will stimulate

the reader to a greater understanding and thereafter a healthy appetite for more knowledge.

The obstetrics and gynaecology of the future will almost certainly be different from the practice that has occurred over the last 150 years and as the future beckons more specialized individuals, a basic knowledge of obstetrics and gynaecology will still underpin the training of young doctors for the future. I hope this book will continue to provide that wealth of knowledge and stimulate young doctors to join the specialty and become contributors in the future.

I would like to thank my secretary, Liz Manson, without whom many of the contributors in this book would have slept very soundly. Her incessant efforts to obtain the chapters have been remarkable and I am indebted to her. I would also like to thank Fiona Pattison at Blackwell Publishing and the editorial team for their support in the publication of this volume.

D. KEITH EDMONDS
2006

Preface to the First Edition

Our purpose in writing this book has been to produce a comprehensive account of what the specialist in training in obstetrics and gynaecology must know. Unfortunately for him, he must now know a great deal, not only about his own subject, but about certain aspects of closely allied specialties such as endocrinology, biochemistry, cytogenetics, psychiatry, etc. Accordingly we have tried to offer the postgraduate student not only an advanced textbook in obstetrics and gynaecology but one which integrates the relevant aspects of other subjects which nowadays impinge more and more on the clinical field.

To achieve this aim within, we hope, a reasonable compass we have assumed some basic knowledge which the reader will have assimilated throughout his medical training, and we have taken matters on from there. Fundamental facts not in question are stated as briefly as is compatible with accuracy and clarity, and discussion is then devoted to more advanced aspects. We acknowledge that it is not possible even in this way to provide all the detail some readers may wish, so an appropriate bibliography is provided with each chapter. Wherever possible we have tried to give a positive opinion and our reasons for holding it, but to discuss nonetheless other important views; this we believe to be more helpful than a complete account of all possible opinions which may be held. We have chosen moreover to lay emphasis on fundamental aspects of the natural and the disease processes which are discussed; we believe concentration on these basic physiological and pathological features to be important to the proper training of a specialist. Clinical matters are, of course, dealt with in detail too, whenever theoretical discussion of them is rewarding. There are, however, some clinical aspects which cannot, at specialist level, be considered in theory with real benefit; examples of these are how to palpate a pregnant woman's abdomen and how to apply obstetric forceps. In general these matters are considered very briefly or perhaps not at all; this is not a book on *how*

things are done, but on how correct treatment is chosen, what advantages one choice has over another, what complications are to be expected, etc. Practical matters, we believe, are better learnt in practice and with occasional reference to specialized textbooks devoted solely to them.

A word may be helpful about the manner in which the book is set out. We would willingly have followed the advice given to Alice when about to testify at the trial of the Knave of Hearts in Wonderland, 'Begin at the beginning, keep on until you come to the end and then stop'. But this advice is difficult to follow when attempting to find the beginning of complex subjects such as those to which this book is devoted. Does the beginning lie with fertilization; or with the events which lead up to it; or with the genital organs upon the correct function of which any pregnancy must depend; or does it lie somewhere else? And which direction must we follow then? The disorders of reproduction do not lie in a separate compartment from genital tract disease, but each is clearly associated with the other for at least part of a woman's life. Although we have attempted to integrate obstetrics with gynaecology and with their associated specialties, some separation is essential in writing about them, and the plan we have followed is broadly this—we begin with the female child *in utero*, follow her through childhood to puberty, through adolescence to maturity, through pregnancy to motherhood, through her reproductive years to the climacteric and into old age. Some events have had to be taken out of order, however, although reiteration has been avoided by indicating to the reader where in the book are to be found other sections dealing with different aspects of any subject under consideration. We hope that our efforts will provide a coherent, integrated account of the field we have attempted to cover which will be to the satisfaction of our readers.

SIR JOHN DEWHURST
1972

Chapter 1: Clinical anatomy of the pelvis and reproductive tract

Alan Farthing

Introduction

This chapter aims to summarize the important aspects of the anatomy of the abdomen and the pelvis, which should be known to the Obstetric or Gynaecological specialist. Many of the investigations and treatments we order on a daily basis require good anatomical knowledge in order to be properly understood.

Surface anatomy

The anterior abdominal wall can be divided into four quadrants by lines passing horizontally and vertically through the umbilicus (Fig. 1.1). In the upper abdomen is the epigastrum, which is the area just inferior to the xiphisternum, and in the lower abdomen lie the right and left iliac fossae and the hypogastrum.

The cutaneous nerve supply of the anterior abdominal wall arises from the anterior rami of the lower thoracic and lumbar vertebrae. The dermatomes of significant

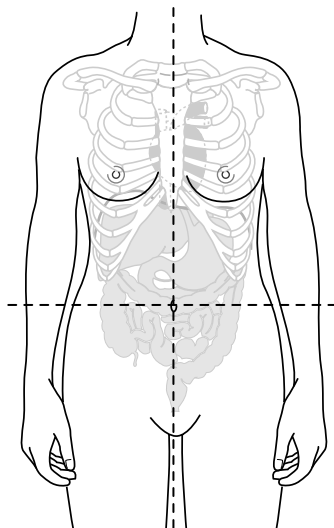


Fig. 1.1 The abdomen can be divided into quadrants.

structures on the anterior abdominal wall are:

T7 xiphisternum

T10 umbilicus

L1 symphysis pubis

The blood supply is via the superior epigastric (branch of the internal thoracic artery) and the inferior epigastric (branch of the external iliac artery) vessels. During laparoscopy, the inferior epigastric vessels can be seen between the peritoneum and rectus muscle on the anterior abdominal wall and commence their journey superiorly from approximately two thirds of the way along the inguinal ligament closer to the symphysis pubis. Care needs to be taken to avoid them while using accessory trochars during laparoscopy and to ensure that they are identified when making a Maylard incision of the abdominal wall.

The anterior abdominal wall

Beneath the skin and the fat of the superficial anterior abdominal wall lies a sheath and combination of muscles including the rectus abdominus, external and internal oblique and transversalis muscles (Fig. 1.2). Where these muscles coalesce in the midline, the linea alba is formed. Pyramidalis muscle is present in almost all women originating on the anterior surface of the pubis and inserting into the linea alba. The exact configuration of the muscles encountered by the surgeon depends on exactly where any incision is made.

The umbilicus

The umbilicus is essentially a scar made from the remnants of the umbilical cord. It is situated in the linea alba and in a variable position depending on the obesity of the patient. However the base of the umbilicus is always the thinnest part of the anterior abdominal wall and is the commonest site of insertion of the primary port in laparoscopy. The urachus is the remains of the allantois from the fetus and runs from the apex of the bladder to the umbilicus.

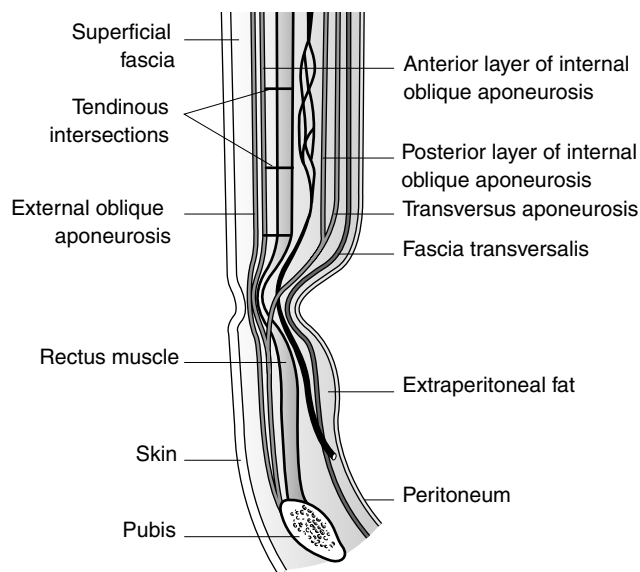


Fig. 1.2 The layers of the anterior abdominal wall in transverse section.

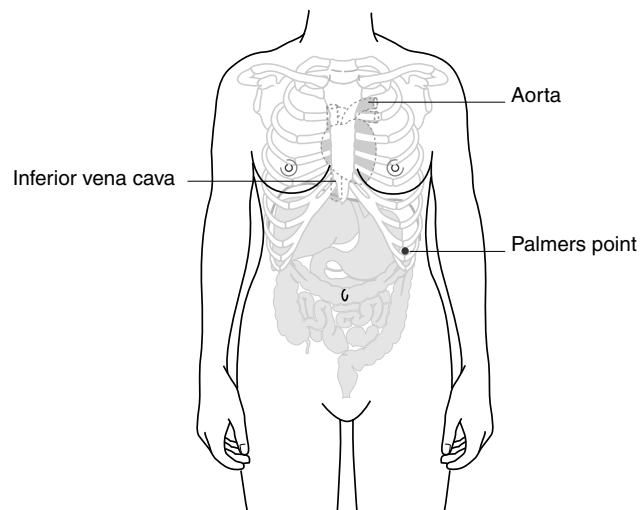


Fig. 1.3 The umbilicus in relation to the underlying vasculature in a thin patient.

Occasionally this can remain patent in newborns. In early embryological life, the vitelline duct also runs through the umbilicus from the developing midgut. Although the duct is severed long before delivery, a remnant of this structure is found in 2% of the population as a Meckels diverticulum.

The aorta divides into the common iliac arteries approximately 1–2 cm below the umbilicus in most slim women (Fig. 1.3). The common iliac veins combine to form the inferior vena cava just below this and all these structures

are a potential hazard for the laparoscopist inserting ports at the umbilicus.

Epithelium of the genital tract

The anterior abdominal wall including the vulva, vagina and perineal areas are lined with squamous epithelium. The epithelium lining the endocervix and uterine cavity is columnar and the squamocolumnar junction usually arises at the ectocervix in women of reproductive age. This is an important site as it is the area from which cervical intraepithelial neoplasia (CIN) and eventually cervical malignancy arises. The bladder is lined by transitional epithelium which becomes columnar. The anal verge is still squamous epithelium but this changes to columnar immediately inside the anus and into the rectum.

The genital tract, from the vagina, through the uterus and out through the fallopian tubes into the peritoneal cavity, is an open passage. This is an essential route for the traversing of sperm in the process of fertilization but unfortunately it also allows the transport of pathologic organisms which may result in ascending infection.

The peritoneum

The peritoneum is a thin serous membrane which lines the inside of the pelvic and abdominal cavities. In simplistic terms it is probably best to imagine a pelvis containing the bladder, uterus and rectum (Fig. 1.4) and note that the peritoneum is a layer placed over these organs in a single sheet. This complete layer is then pierced by both the fallopian tubes and the ovaries on each side. Posteriorly the rectum also pierces the peritoneum connecting to the sigmoid colon and the area between the posterior surface of the uterus and its supporting ligaments and the rectum is called the Pouch of Douglas. This particular area is important in gynaecology as the place where gravity dependent fluid collects. As a result this is where blood is found in ectopic pregnancies, pus in infections and endometriosis which has been caused by retrograde menstruation (Sampsons theory).

Vulva

The vulva is the area of the perineum including the Mons pubis, labia majora and minora and the opening into both the vagina and urethra (Fig. 1.5). The labia majora are areas of skin with underlying fat pads which bound the vagina. Medial to these are the labia minora which consist of vascular tissue which reacts to the stimulation of sexual arousal. Anteriorly they come together to form the prepuce of the clitoris and posteriorly they form the forchette.

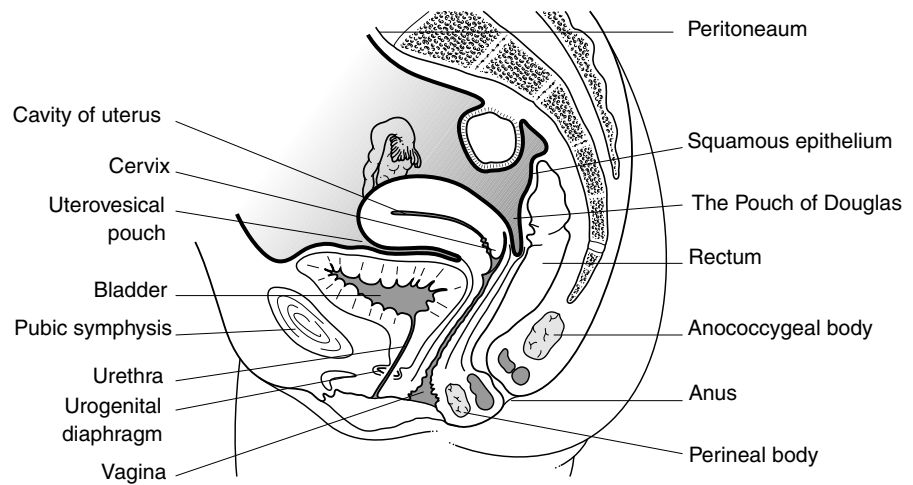


Fig. 1.4 Transverse view of the pelvic organs.

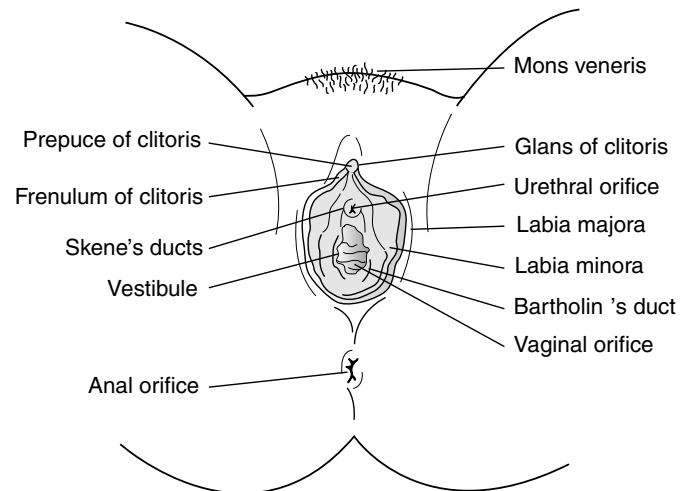


Fig. 1.5 Surface anatomy of the vulva.

The hymen is a fold of vaginal mucosa at the entrance to this organ. It usually has a small opening in virgins and is only seen as an irregular remnant in sexually active women.

To each side of the introitus are the ducts of the vestibular glands commonly known as Bartholin's glands which produce much of the lubrication at sexual intercourse.

The vulval blood supply comes from the pudendal artery and lymphatic drainage is through the inguinal lymph nodes. The nerve supply comes mostly from the pudendal nerve and pelvic plexus with branches of the perineal nerves and posterior cutaneous nerve of the thigh important in the posterior region.

The clitoris

The clitoris corresponds to the male penis consisting of the same three masses of erectile tissue (Fig. 1.6). The bulb

of the vestibule is attached to the underlying urogenital diaphragm and split into two because of the presence of the vagina. The right and left crura become the corpora cavernosa and are covered by the ischiocavernosus muscles.

Bony pelvis

The bony pelvis consists of two hip bones (consisting of the ileum and ischium) which are joined together by the sacrum posteriorly and the symphysis pubis anteriorly (Figs. 1.7 and 1.8). In addition, the coccyx lies on the inferior aspect of the sacrum. A plane drawn between the sacral promontory and the superior aspect of the symphysis pubis marks the pelvic inlet and a similar plane drawn from the tip of S5 to the inferior aspect of the symphysis pubis marks the pelvic outlet.

Clinically the ischial spine is important as it can be felt vaginally and progress in labour can be measured using it as a landmark. Additionally it is an insertion point of the sacrospinous ligament which also attaches to the lower lateral part of the sacrum. Together with the sacrotuberous ligament and the bony pelvis, it forms the borders of the greater sciatic foramen (through which the sciatic nerve passes) and the lesser sciatic foramen (through which the pudendal nerve enters the pelvis).

The sacrum and ilium are joined by the very strong sacroiliac joint. This is a synovial joint and is supported by the posterior and interosseous sacroiliac ligaments. The symphysis pubis is a cartilaginous joint with a fibrocartilaginous disc separating the two bones which are firmly bound together by the supporting ligaments. There should be virtually no movement of this joint.

Pelvic floor (Figs. 1.9 and 1.10)

The obturator internus muscle sits on the medial side of the ischial bone and, together with the body of the pubis, forms a wall that supports the origins of the pelvic floor. The pelvic floor itself is a sling of various muscles which are pierced by the urethra, the vagina and the anal canal. Posterior to the vagina these muscles form the perineal body. The puborectalis muscle forms a sling around the junction of the anus and rectum and posterior to the anus, these fibres are made up by the pubococcygeus which forms the anococcygeal body in the midline (Fig. 1.9). The collection of muscles is variously referred to as the pelvic diaphragm or levator ani muscles (Fig. 1.10). These muscles support the pelvic organs, holding them in position and resisting the forces created when the intraperitoneal

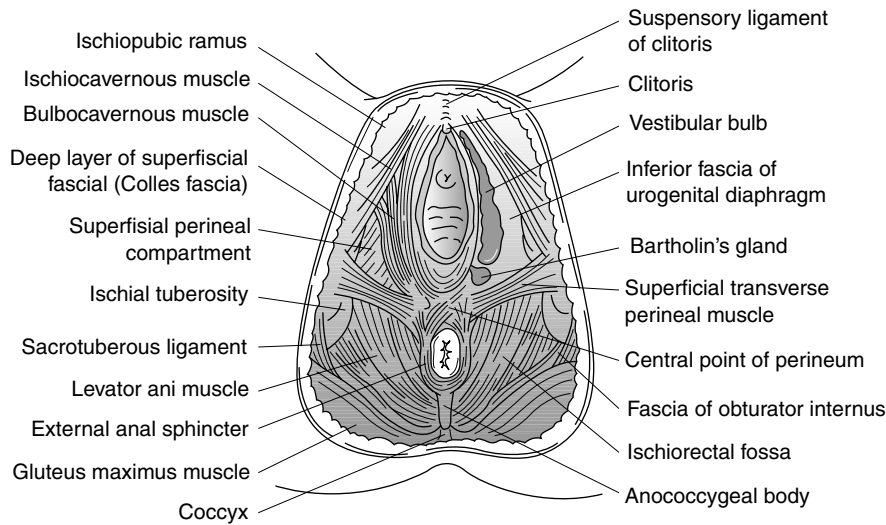


Fig. 1.6 The deeper vulval tissues.

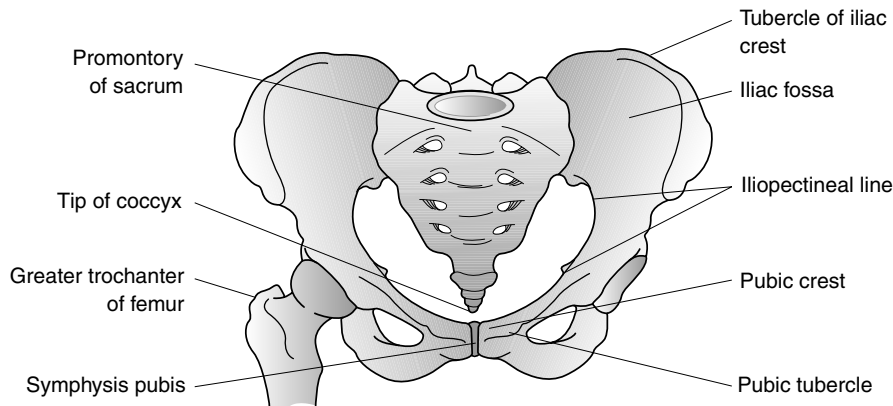


Fig. 1.7 Bony pelvis.

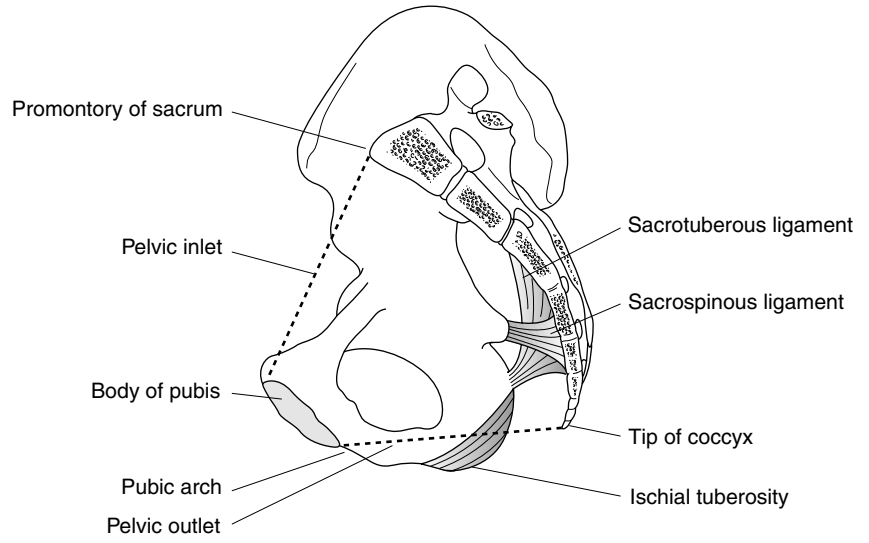


Fig. 1.8 Bony pelvis.

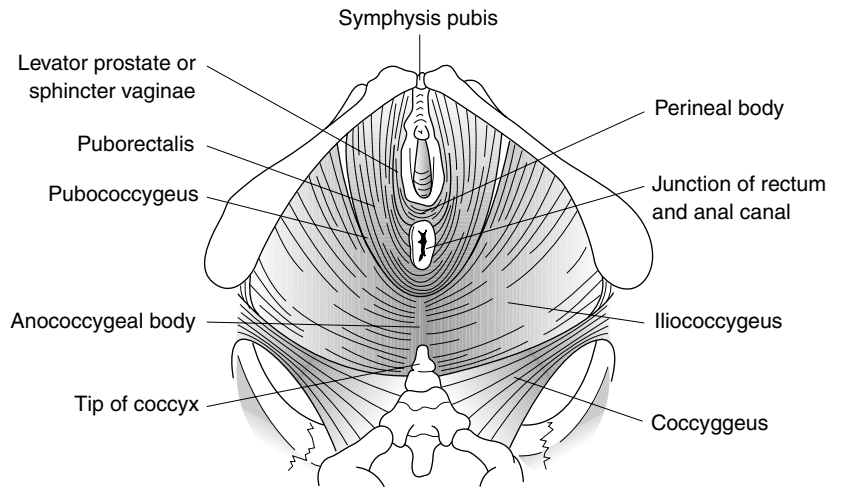


Fig. 1.9 Pelvic floor muscles.

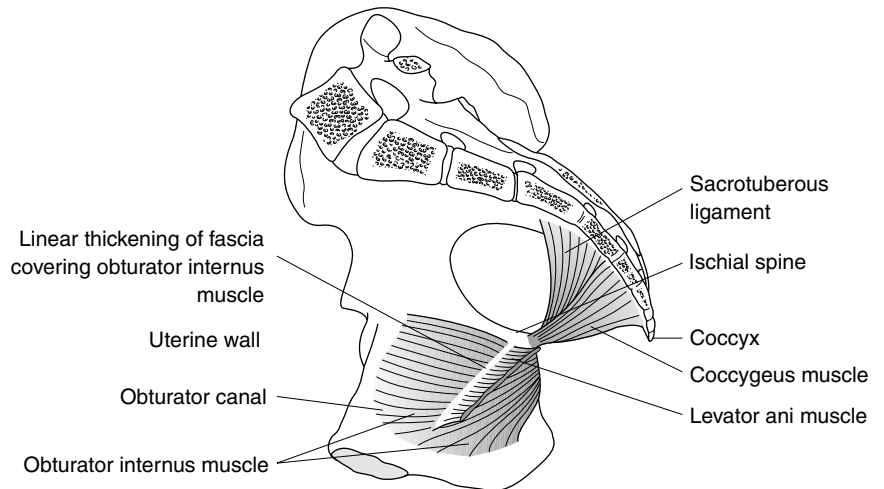


Fig. 1.10 Transverse view of the pelvic floor muscles.



Fig. 1.11 MRI of the pelvis.

pressure is raised as in coughing or straining. The nerve supply is from the fourth sacral nerve and pudendal nerve.

Pelvic organs (Fig. 1.11)

Vagina

The vagina is a distensible muscular tube which passes from the introitus to the cervix. It pierces the pelvic floor and then lies flat on its posterior surface using it as support. It is approximately 8 cm long and the anterior and posterior walls oppose each other. Anatomical text books can give a confusing impression when showing this structure as an open tube with a lumen. However, on imaging, the normal vagina should not be distended and does not contain air. Projecting into the top of the vagina is the uterine cervix. The areas of the vagina which border the cervix are referred to as the fornices and are labelled as anterior, posterior, right or left.

The vaginal wall consists of outer and inner circular layers of muscles which cannot be distinguished from each other. The epithelium contains no glands but is rich in glycogen in the premenopausal woman. The normal commensal, *Doderleins bacillus*, breaks down this glycogen to create an acid environment.

Uterus

The uterus is approximately the size and shape of a pear with a central cavity and thick muscular walls (Fig. 1.12).

The serosal surface is the closely applied peritoneum beneath which is the myometrium which is a smooth muscle supported by connective tissue. The myometrium is made up of three layers of muscle, external, intermediate and internal layers. Clinically this is important as fibroids leave the layers intact and removal through a superficial incision leaves the three layers intact. The three layers run in complimentary directions which encourage vascular occlusion during contraction, an important aspect of menstrual blood loss and postpartum haemostasis. The mucous membrane overlying the myometrium to line the cavity is the endometrium. Glands of the endometrium pierce the myometrium and a single layer of columnar epithelium on the surface changes cyclically in response to the menstrual cycle.

The uterus consists of a fundus superiorly, a body, an isthmus (internal os) and inferiorly the cervix (external os). The cervix is a cylindrical structure which is muscular in its upper portions but this gives way to fibrous connective tissue as the cervix sits at the top of the vagina. The cervix is lined by columnar epithelium, which secretes alkaline mucus neutralizing the effects of vaginal acidity.

The cervix and uterus do not always sit in the same plane and when the uterine body rotates anteriorly it is referred to as anteflexed and posteriorly as retroflexed. The axis of the entire uterus can be anteverted or retroverted in relation to the axis of the vagina (Fig. 1.13).

The uterus is supported by the muscles of the pelvic floor together with three supporting condensations of connective tissue. The pubocervical ligaments run from the cervix anteriorly to the pubis, the cardinal ligaments pass laterally from the cervix and upper vagina to the lateral pelvic side walls and the uterosacral ligaments from the cervix and upper vagina to the sacrum. These uterosacral ligaments can be clearly seen posterior to the uterus in the Pouch of Douglas and are a common site for superficial and deep infiltrating endometriosis.

The uterine blood supply is derived mainly from the uterine artery, a branch of the anterior division of the internal iliac artery. An anastomosis occurs with the blood supply delivered through the ovarian ligament and derived direct from the ovarian artery.

The round ligament is the remains of the gubernaculum and extends from the uterus laterally to the pelvic side wall and then into the inguinal canal before passing down into the labia majora. It holds the uterus in anteversion, although it is a highly distensible structure in pregnancy. It is usually the first structure divided at hysterectomy allowing the surgeon to open the overlying folds of peritoneum known as the broad ligament.

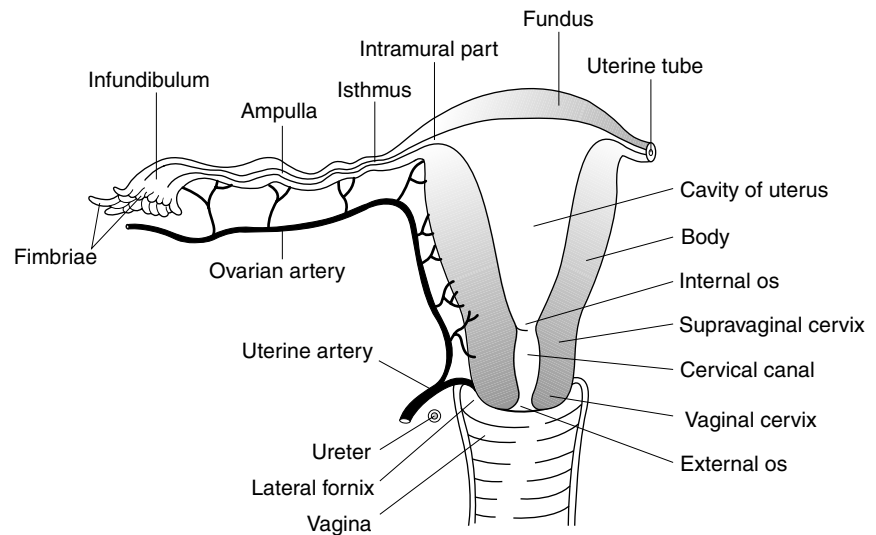


Fig. 1.12 Uterus and fallopian tubes.

Fallopian tubes

The fallopian tubes are delicate tubular structures which carry the ovum or sperm between the ovary and uterine cavity. The tubes are divided into named regions, most medially the cornu and interstitial portion within the uterine wall, then the isthmus followed by the infundibulum, ampulla and finally fimbrial ends. They are lined by columnar epithelium and cilia which together with the peristaltic action of the surrounding smooth muscle propel the fertilized ovum towards the uterine cavity. The blood supply of the fallopian tubes arises from both the uterine and ovarian arteries through the mesosalpinx which is covered by peritoneum.

Ovaries

The ovaries vary in size depending on age and their function. They are approximately $2 \times 4 \text{ cm}^2$ with the long axis running vertically and are attached to the posterior leaf of the broad ligament by the mesovarium. In addition they are fixed in position by the ovarian ligament (to the uterus medially) and the infundibulopelvic ligament which contains the ovarian blood supply direct from the aorta. Venous drainage is to the ovarian veins which drain direct into the inferior vena cava on the right and into the renal vein on the left. The aortic nerve plexus also accompanies the ovary in its descent from around the level of the first lumbar vertebra.

The lateral pelvic side wall is covered by peritoneum which is folded to form the ovarian fossa. Pathological adhesions around the ovary will often cause it to be

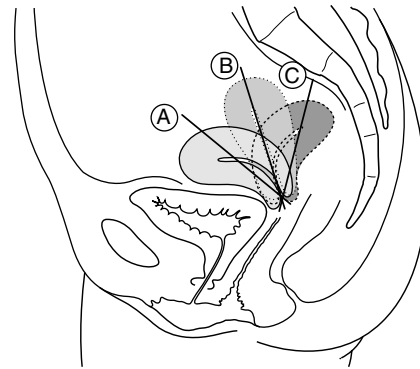


Fig. 1.13 The axis of the uterus in relation to the vagina.

fixed into the ovarian fossa causing cyclical pain or dyspareunia.

The ovary is not covered by peritoneum but is surrounded by a thin membranous capsule, the tunica albuginea, which in turn is covered by the germinal epithelium.

Bladder

The urinary bladder is situated immediately behind the pubic bone and anterior to the uterine cervix and upper vagina. It has a strong muscular wall consisting of three layers of interlacing fibres which are known together as the detrusor muscles (Fig. 1.14). The trigone is the only smooth part of the bladder as it is fixed to the underlying muscle. At the superior margins of the trigone lie the ureteric openings and at the inferior aspect the urethra.

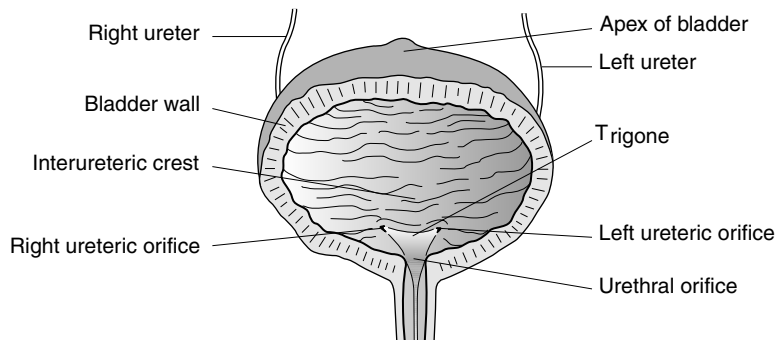


Fig. 1.14 The bladder.

An interureteric ridge can often be visualized horizontally between the ureters at cystoscopy and is useful for orientation.

The rest of the bladder is highly distensible ensuring that as it is expanded the pressure of its contents remains the same.

The bladder receives its blood supply from the superior and inferior vesical arteries which originate from the internal iliac artery. The nerve supply is from the inferior hypogastric plexus. Sympathetic nerves arise in the first and second lumbar ganglia and the parasympathetic supply from the splanchnic nerves of the second, third and fourth sacral nerves.

URETHRA

The urethra is approximately 4 cm long in the female adult starting at the internal meatus of the bladder and passing through the pelvic floor to the vestibule. The epithelium is squamous near the external meatus and changes to transitional epithelium about two thirds of the way to the bladder. The deeper tissue is muscular and this maintains the urethral tone. There are no anatomical sphincters but the muscle fibres of the bladder at the internal meatus act as an 'internal sphincter' and the pelvic floor as a voluntary external sphincter.

URETERS

The ureters run from the renal hilum to the trigone of the bladder and are approximately 30 cm in length. They enter the pelvis by passing over the common iliac bifurcation at the pelvic brim. They then pass along the lateral pelvic side wall before passing anteriorly and medially under the uterine artery as it originates from the internal iliac artery and into the base of the bladder. The ureter comes close to the ovarian artery and vein and can be adherent to these vessels or the overlying ovary in pathological

cases. By passing close to the uterine artery it can be mistakenly clamped and divided as a rare complication of hysterectomy.

The ureters are muscular tubes lined by transitional epithelium. The blood supply varies during its course but small vessels along the surface of the ureter require careful preservation when dissecting it free from other structures.

Rectum

The rectum is approximately 12 cm in length and starts at the level of S3 as a continuation of the sigmoid colon. The puborectalis part of the pelvic floor forms a sling around the lower end at the junction with the anal canal. The rectum is commonly depicted in anatomic drawing as being dilated, causing the other pelvic organs to be pushed forward. This is because the original drawings were taken from cadavers but in the live patient the rectum is often empty allowing the other structures to lie supported on the pelvic floor.

The mucosa of the rectum is columnar and this is surrounded by inner circular and outer longitudinal fibres of smooth muscle. The serosal surface is covered by peritoneum.

The blood supply is from the superior rectal artery from the inferior mesenteric artery, and the middle and inferior rectal arteries arise from the posterior division of the internal iliac artery. The nerve supply is from the inferior hypogastric plexus and ensures the rectum is sensitive to stretch only.

Conclusion

A clear knowledge of anatomy is required for many gynaecological diagnoses and certainly for surgery. Many clinicians do not gain a full understanding of pelvic anatomy until they start operating and then

rarely refer back to anatomical textbooks. The advent of more sophisticated pelvic floor surgery and especially minimal access surgery has modified the skills required of a gynaecological surgeon which necessitates the need for greater practical anatomical knowledge.

Further reading

Shah Farthing & Richardson Lennard (2003) *The Interactive Pelvis & Perineum: Female*. Primal Pictures Ltd, www.primalpictures.com
Snell R. *Clinical Anatomy for Medical Students*. London: Little Brown & Co.

Chapter 2: Maternal physiology

Fiona Broughton-Pipkin

The physiological changes of pregnancy are strongly proactive, not reactive, with the luteal phase of every ovulatory menstrual cycle ‘rehearsing’ for pregnancy [1]. Most pregnancy-driven changes are qualitatively in place by the end of the first trimester, only maturing in magnitude thereafter. This chapter gives a brief overview of the major changes.

The cardiovascular system

There is a significant fall in total peripheral resistance by 6 weeks gestation to a nadir of ~40% by mid-gestation, resulting in a fall in afterload. This is ‘perceived’ as circulatory underfilling, which activates the renin-angiotensin-aldosterone system and allows the necessary expansion of the plasma volume (PV; Fig. 2.1) [2,3]. By the late third trimester, the PV has increased from its baseline by about

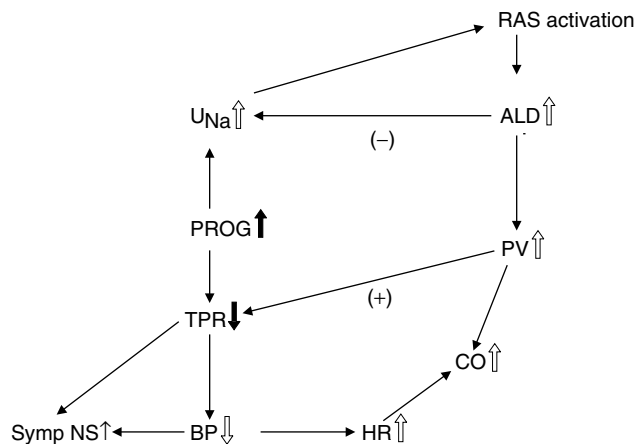


Fig. 2.1 Flow chart of the probable sequence of initial cardiovascular activation. ALD, aldosterone; BP, systemic arterial blood pressure; CO, cardiac output; HR, heart rate; PROG, progesterone; PV, plasma volume; RAS, renin-angiotensin system; Symp NS, sympathetic nervous system; TPR, total peripheral resistance; U_{Na}, urinary sodium excretion.

50% in a first pregnancy and 60% in a second or subsequent pregnancy. The bigger the expansion is, the bigger, on average, the birthweight of the baby. The total extracellular fluid volume rises by about 16% by term, so the percentage rise in PV is disproportionate to the whole. The plasma osmolality falls by ~10 mOsm/kg as water is retained.

The heart rate rises synchronously, by 10–15 b.p.m., so the cardiac output begins to rise [4]. There is probably a fall in baroreflex sensitivity as pregnancy progresses and heart rate variability falls. Stroke volume rises a little later in the first trimester. These two factors push the cardiac output up by 35–40% in a first pregnancy, and ~50% in later pregnancies; it can rise by a further third in labour (Fig. 2.2). Table 2.1 summarizes the percentage changes in some cardiovascular variables during pregnancy.

Measuring systemic arterial blood pressure in pregnancy is notoriously difficult, but there is now broad consensus that Korotkoff 5 should be used with auscultatory techniques [5]. However measured, there is a small fall in systolic and a greater fall in diastolic blood pressure during the first half of pregnancy resulting in an increased pulse pressure. The blood pressure then rises steadily and, even in normotensive women, there is some late overshoot of non-pregnant values. Supine hypotension occurs in ~8% of women in late gestation.

The pressor response to angiotensin II (ANG II) is reduced in normal pregnancy but is unchanged to noradrenaline. The reduced sensitivity to ANG II presumably protects against the potentially pressor levels of ANG II found in normal pregnancy and is associated with lower receptor density; plasma noradrenaline is not increased in normal pregnancy. Pregnancy does not alter the response of intramyometrial arteries to a variety of vasoconstrictors. Nitric oxide may modulate myogenic tone and flow-mediated responses in the resistance vasculature of the uterine circulation in normal pregnancy.

The venous pressure in the lower circulation rises for both mechanical and hydrodynamic reasons. The pulmonary circulation is able to absorb high rates of flow without an increase in pressure; so pressure in the right

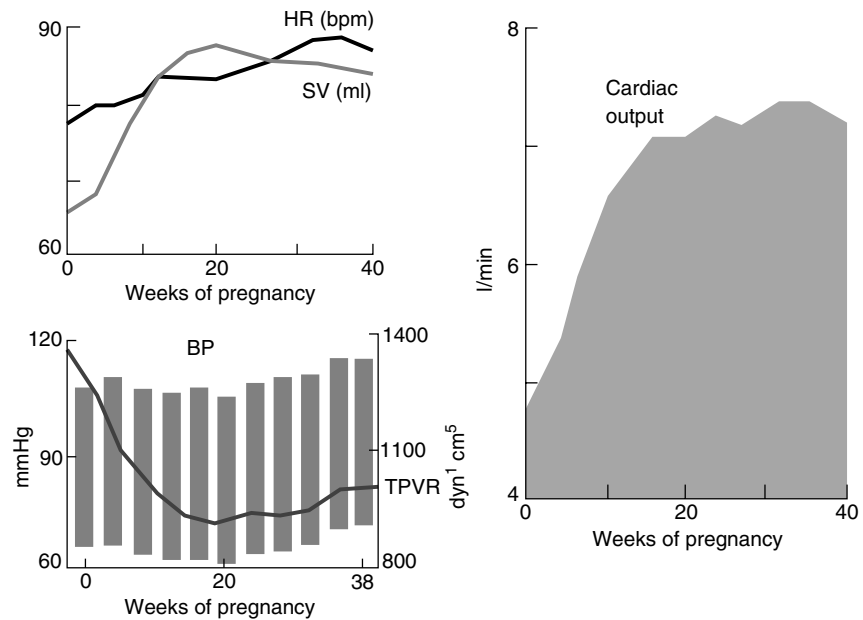


Fig. 2.2 Major haemodynamic changes associated with normal human pregnancy. The marked augmentation of cardiac output results from asynchronous increases in both heart rate (HR) and stroke volume (SV). Despite the increases in cardiac output, blood pressure (BP) decreases for most of pregnancy. This implies a very substantial reduction in total peripheral vascular resistance (TPVR).

Table 2.1 Percentage change in some cardiovascular variables during pregnancy

	First trimester	Second trimester	Third trimester
Heart rate (bpm)	+11	+13	+16
Stroke volume (ml)	+31	+29	+27
Cardiac output (l/min)	+45	+47	+48
Systolic BP (mmHg)	-1	+1	+6
Diastolic BP (mmHg)	-6	-3	+7
MPAP (mmHg)	+5	+5	+5
Total peripheral resistance (resistance units)	-27	-27	-29

BP, systemic blood pressure; MPAP, mean pulmonary artery pressure. Data are derived from studies in which pre-conception values were determined. The mean values shown are those at the end of each trimester, and are thus not necessarily the maxima. Note that most changes are near maximal by the end of the first trimester. (Data from Robson *et al.*, 1991.)

ventricle and the pulmonary arteries and capillaries does not change. Pulmonary resistance falls in early pregnancy and does not change thereafter. There is progressive venodilatation and rises in venous distensibility and capacitance throughout a normal pregnancy, possibly because of increased local nitric oxide synthesis.

The respiratory system

Tidal volume rises by ~30% in early pregnancy to 40–50% above non-pregnant values by term, with a fall in expiratory reserve and residual volume (Fig. 2.3) [6]. Neither FEV₁ nor peak expiratory flow rate are affected by

pregnancy, even in women with asthma. The rise in tidal volume is largely driven by progesterone, which appears to decrease the threshold and increase the sensitivity of the medulla oblongata to carbon dioxide. Respiratory rate does not change, so the minute ventilation rises by a similar amount. This overbreathing also begins before conception; the P_{CO_2} is lowest in early gestation. Progesterone also increases erythrocyte [carbonic anhydrase], which will also lower P_{CO_2} . Carbon dioxide production rises sharply during the third trimester, as fetal metabolism increases. The fall in maternal P_{CO_2} allows more efficient placental transfer of carbon dioxide from the fetus, which has a P_{CO_2} of around 55 mmHg (7.3 kPa). The fall in P_{CO_2} results in a fall in plasma bicarbonate concentration (to ~18–22 mmol/l by comparison with 24–28 mmol/l) which contributes to the fall in plasma osmolality; the peripheral venous pH rises slightly (Table 2.2; Fig. 2.4).

The increased alveolar ventilation results in a much smaller proportional rise in P_{O_2} , from around 96.7 to 101.8 mmHg (12.9–13.6 kPa). This increase is offset by the rightward shift of the maternal oxyhaemoglobin dissociation curve caused by an increase in 2,3-diphosphoglycerate (2,3-DPG) in the erythrocytes. This facilitates oxygen unloading to the fetus, which has both a much lower P_{O_2} (25–30 mmHg; 3.3–4.0 kPa) and a marked leftwards shift of the oxyhaemoglobin dissociation curve, due to the lower sensitivity of fetal haemoglobin to 2,3-DPG.

There is an increase of ~16% in oxygen consumption by term, due to increasing maternal and fetal demands. Since the increase in oxygen-carrying capacity of the blood (see 'Haematology', p. 12) is ~18%, there is actually a

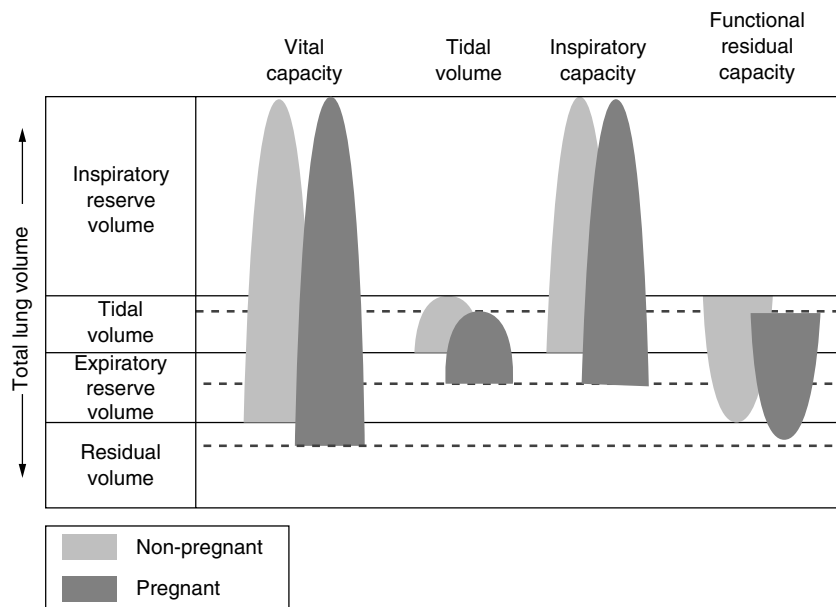


Fig. 2.3 Alterations in lung volumes associated with normal human pregnancy. In general terms, inspiratory reserve and tidal volumes increase at the expense of expiratory reserve and residual volumes.

Table 2.2 The influence of pregnancy on some respiratory variables

		Non-pregnant	Pregnant – term
P_{O_2}	mmHg (kPa)	93 (12.5)	102 (13.6)
O_2 consumption	ml/min	200	250
P_{CO_2}	mmHg (kPa)	35–40 (4.7–5.3)	30 (4.0)
Venous pH		7.35	7.38

Table 2.3 Although the increases in resting cardiac output and minute ventilation are of the same order of magnitude in pregnancy, there is less spare capacity for increases in cardiac output on moderate exercise than for increases in respiration

	Resting	Exercise
Cardiac output	+33% (4.5–6 l/min)	+167% (up to 12 l/min)
Minute ventilation	+40% 7.5–10.5 l/min	+1000% (up to ~80 l/min)

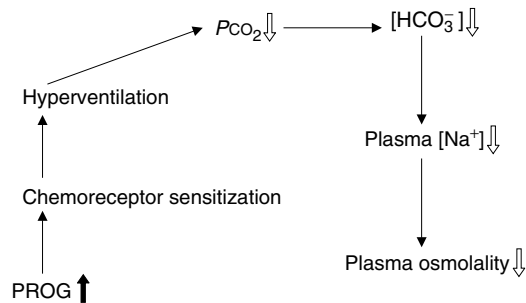


Fig. 2.4 Flow chart of the effects of over-breathing. HCO_3^- , bicarbonate; Na, sodium; P_{CO_2} , carbon dioxide tension; PROG, progesterone.

fall in arterio-venous oxygen difference. Pulmonary blood flow, of course, rises in parallel with cardiac output and enhances gas transfer.

Pregnancy places greater demands on the cardiovascular than the respiratory system [7]. This is shown in the response to moderate exercise (Table 2.3).

Haematology

The circulating red cell mass increases by 20–30% during pregnancy, with rises in both cell number and size. It rises more in women with multiple pregnancies, and substantially more with iron supplementation (~29% compared with 17%). Serum iron concentration falls, the absorption of iron from the gut rises and iron-binding capacity rises in a normal pregnancy, since there is increased synthesis of the β_1 -globulin, transferrin. Plasma folate concentration halves by term, because of greater renal clearance, although red cell folate concentrations fall less. Even now, only ~20% of fertile women in the UK have adequate iron reserves for a pregnancy and ~40% have virtually no iron stores. Even relatively mild maternal anaemia is associated with increased placental:birthweight ratios and decreased birthweight. However, inappropriate supplementation can itself be associated with pregnancy problems [8]. Erythropoietin rises in pregnancy, more if iron supplementation is not taken (55% compared with 25%) but the

changes in red cell mass antedate this; human placental lactogen may stimulate haematopoiesis.

Pro rata, the plasma volume increases more than the red cell mass, which leads to a fall in the various concentration measures which include the plasma volume, such as the haematocrit, the haemoglobin concentration and the red cell count. The fall in packed cell volume from ~36% in early pregnancy to ~32% in the third trimester is a sign of normal plasma volume expansion.

The total white cell count rises, mainly because of increased polymorphonuclear leucocytes. Neutrophil numbers rise with oestrogen concentrations and peak at ~33 weeks stabilizing after that until labour and the early puerperium, when they rise sharply. Their phagocytic function increases during gestation. T and B lymphocyte counts do not change but their function is suppressed, making pregnant women more susceptible to viral infections, malaria and leprosy. The uterine natural killer cells express receptors that recognize the otherwise anomalous combination of human lymphocyte antigens (HLA-C, -E and -G) expressed by the invasive cytotrophoblasts. This is likely to be central to the maternal recognition of the conceptus [9].

Platelet count and platelet volume are largely unchanged in most pregnant women, although their survival is reduced. Platelet reactivity is increased in the second and third trimesters and does not return to normal until ~12 weeks after delivery.

Coagulation

Continuing low-grade coagulopathy is a feature of normal pregnancy [10]. Several of the potent procoagulatory factors rise from at least the end of the first trimester (Fig. 2.5). For example, Factors VII, VIII and X all rise and absolute plasma fibrinogen doubles, while antithrombin III, an inhibitor of coagulation, falls. The erythrocyte sedimentation rate rises early in pregnancy due to the increase in fibrinogen and other physiological changes. Protein C, which inactivates Factors V and VIII, is probably unchanged in pregnancy, but concentrations of Protein S, one of its co-factors, fall during the first two trimesters. An estimated 5–10% of the total circulating fibrinogen is consumed during placental separation, and thromboembolism is the main cause of maternal death in the UK. Plasma fibrinolytic activity is decreased during pregnancy and labour, but returns to non-pregnant values within an hour of delivery of the placenta, suggesting strongly that the control of fibrinolysis during pregnancy is significantly affected by placentally derived mediators. Table 2.4 summarizes changes in some coagulation and fibrinolytic variables during pregnancy.

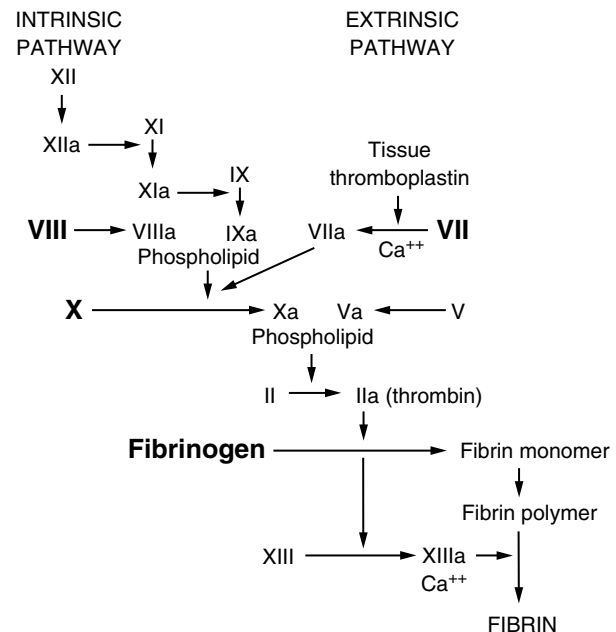


Fig. 2.5 Alterations in the coagulation pathways associated with human pregnancy. Factors which increase during normal pregnancy are printed in bold type.

Table 2.4 Percentage changes in some coagulation (upper) and fibrinolytic variables and fibronectin levels are expressed from postpartum data in the same women

	First trimester	Second trimester	Third trimester
PAI-1 (mg/ml)	-10	+68	+183
PAI-2 (mg/ml)	+732	+1804	+6554
t-PA (mg/ml)	-24	-19	+633
Protein C (% activity)	-12	+10	+9
AT III (% activity)	-21	-14	-10
TAT III	+362	+638	+785
Fibronectin (mg/l)	+3	-12	+53

PAI-1 and PAI-2, plasminogen activator inhibitors 1 and 2; t-PA, tissue plasminogen activator antigen; AT III, antithrombin III; TAT III, thrombin-antithrombin III complex.

The mean values shown are those at the end of each trimester, and are thus not necessarily the maxima. Note the very large rises in PAI-2 (placental type PAI) and TAT III complexes in the first trimester. (Data from Halligan *et al.* 1994)

The renal system

The kidneys increase in size in pregnancy mainly because renal parenchymal volume rises by about 70% with marked dilatation of the calyces, renal pelvis and ureters in most women [11]. Ureteric tone does not decrease, but bladder tone does. The effective renal plasma flow (RPF) is increased by at least 6 weeks gestation and rises to some

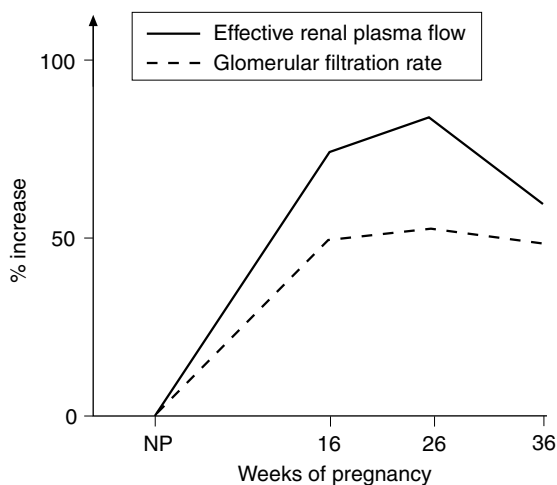


Fig. 2.6 The changes in renal function during pregnancy are largely complete by the end of the first trimester, and are thus pro-active, not reactive to the demands of pregnancy. The filtration fraction falls during the first trimester, but begins to return to non-pregnant levels during the third trimester. With permission from [11].

80% by mid-pregnancy falling thereafter to ~65% above non-pregnant values (Fig. 2.6). This increase is proportionally greater than the increase in cardiac output, presumably reflecting specific vasodilatation, probably via the increased renal prostacyclin synthesis. The glomerular filtration rate (GFR) also increases, by ~45% by the 9th week, only rising thereafter by another 5–10%, but this is largely maintained to term, so the filtration fraction falls during the first trimester, is stable during the second, and rises towards non-pregnant values thereafter. These major increments do not, however, exhaust the renal reserve. This differential changes in ERPF and GFR in late pregnancy suggest a mechanism acting preferentially at the efferent arterioles, possibly angiotensin II.

The filtered load of metabolites therefore increases markedly, and reabsorptive mechanisms frequently do not keep up (e.g. glucose and aminoacids; see below). These changes have profound effects on the concentration of certain plasma metabolites and electrolytes and 'Normal' laboratory reference ranges may thus be inappropriate in pregnancy. For example, plasma creatinine falls significantly by the 4th week of gestation and continues to fall to mid-pregnancy, to below 50 $\mu\text{mol/l}$, but creatinine clearance begins to fall during the last couple of months of pregnancy, so plasma creatinine rises again.

Total body water rises by about 20% during pregnancy (~8.5 l) with a very sharp fall in plasma osmolality between weeks 4–6 after conception, possibly through the actions of hCG. The volume-sensing arginine vasopressin (AVP) release mechanisms evidently adjust as pregnancy

progresses. As well as water present in the fetus, amniotic fluid, placenta and maternal tissues, there is also oedema fluid and increased hydration of the connective tissue ground substance with laxity and swelling of connective tissue.

The pregnant woman accumulates some 950 mmol sodium in the face of high circulating progesterone concentrations which competes with aldosterone at the distal tubule. The potentially natriuretic prostacyclin also rises markedly, with a small rise in atrial natriuretic peptide (ANP). This stimulates the renin-angiotensin system (RAS) with increased synthesis and release of aldosterone from the first trimester. The raised plasma prolactin concentration may also contribute to sodium retention. It is assumed that glomerulotubular balance must also change in pregnancy, to allow the sodium retention which actually occurs. There is a fall of some 4–5 mmol/l in plasma sodium by term, but plasma chloride does not change. Curiously, some 350 mmol potassium is also retained during pregnancy, in the face of the much-increased GFR, substantially raised aldosterone concentrations and a relatively alkaline urine. Renal tubular potassium reabsorption evidently adjusts appropriately to the increased filtered potassium load.

Serum uric acid concentration falls by about a quarter in early pregnancy, with an increase in its fractional excretion secondary to a decrease in net tubular reabsorption. The kidney excretes a progressively smaller proportion of the filtered uric acid, so a rise in serum uric acid concentration during the second half of pregnancy is normal. A similar pattern is seen in relation to urea, which is also partly reabsorbed in the nephron.

Glucose excretion may rise 10-fold as the greater filtered load exceeds the proximal tubular T_{max} for glucose (~1.6–1.9 mmol/min). If the urine of pregnant women is tested sufficiently often, glycosuria will be detected in 50% of them. The excretion of most amino acids increases, which is curious since these are used by the fetus as the building blocks from which it synthesises protein. The pattern of excretion is not constant and differs between individual amino acids. Excretion of the water-soluble vitamins is also increased. The mechanism for all these is inadequate tubular reabsorption in the face of a 50% rise in GFR.

Urinary calcium excretion is also two to threefold higher in normal pregnancy than in the non-pregnant woman, even though tubular reabsorption is enhanced, presumably under the influence of the increased concentrations of 1,25-dihydroxyvitamin D. To counter this, intestinal absorption doubles by 24 weeks, after which it stabilizes. Renal bicarbonate reabsorption and hydrogen ion excretion appear to be unaltered during pregnancy. Pregnant women can acidify their urine, but in pregnancy it is mildly alkaline.